

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Stavenhagen, Jeffrey *et al.*

Appl. No. **10/754,922**

Filed: **January 9, 2004**

For: **Identification and Engineering of
Antibodies with Variant Fc
Regions and Methods of Using
Same**

Art Unit: **1643**

Examiner: **Crowder, Chun**

Atty. Docket: **1301.0004C**

Confirmation No.: **8663**

**Supplemental Information Disclosure Statement
Pursuant to 37 C.F.R. § 1.97(b)(1)**

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Listed on accompanying substitute Form PTO SB08 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. Documents C01-C144 have been previously submitted, but are listed on the accompanying substitute Form PTO SB08 because their titles had not been previously provided to the Examiner. Copies of newly cited documents C145-C147 are submitted herewith.

- C145 Armstrong, S. *et al.* "Heterogeneity of IgG1 monoclonal anti-Rh(D): an investigation using ADCC and macrophage binding assays," Brit. J. Haematol. 66:257-262 (1987)
- C146 Kumpel, B.M. Brit. "Human monoclonal anti-D antibodies," J. Haematol. 71:415-420 (1989)
- C147 Wiener, E. *et al.* "Differences between the activities of human monoclonal IgG1 and IgG3 anti-D antibodies of the Rh blood group system in their abilities to mediate effector functions of monocytes," Immunol. 65:159-163 (1988)

The Examiner is requested to contact the undersigned immediately in the event that any cited document may be unavailable, in order that a replacement copy can be provided.

The newly and previously submitted documents are:

Cite No.	Document Number Patent Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
A01	US- 2003/0158389	08/21/03	Idusogic <i>et al.</i>
A02	US- 2004/0002587	1/1/04	Watkins <i>et al.</i>
A03	US- 2004/0110226	6/10/04	Lazar <i>et al.</i>
A04	US- 2004/0132101	7/8/04	Lazar <i>et al.</i>
A05	US- 2004/0185045	9/23/04	Koenig <i>et al.</i>
A06	US- 2005/0054832	3/10/05	Lazar <i>et al.</i>
A07	US- 4,752,601	06/21/88	Hahn
A08	US- 5,348,876	09/20/94	Michaelson <i>et al.</i>
A09	US- 5,576,184	11/19/96	Better <i>et al.</i>
A10	US- 5,585,089	12/17/96	Queen <i>et al.</i>
A11	US- 5,624,821	4/29/97	Winter <i>et al.</i>
A12	US- 5,648,260	07/15/97	Winter <i>et al.</i>
A13	US- 5,698,449	12/16/97	Baumann <i>et al.</i>
A14	US- 5,723,584	3/3/98	Schatz
A15	US- 5,736,135	4/7/98	Goeddel <i>et al.</i>
A16	US- 5,736,137	04/07/98	Anderson <i>et al.</i>
A17	US- 5,874,239	2/23/99	Schatz
A18	US- 5,932,433	8/3/99	Schatz
A19	US- 5,985,599	11/16/99	Mckenzie <i>et al.</i>
A20	US- 6,025,485	2/15/00	Kamb <i>et al.</i>
A21	US- 6,114,147	9/5/00	Frenken <i>et al.</i>
A22	US- 6,165,745	12/26/00	Ward <i>et al.</i>
A23	US- 6,194,551	2/27/01	Idusogic <i>et al.</i>
A24	US- 6,242,195	06/05/01	Idusogic <i>et al.</i>
A25	US- 6,277,375	08/21/01	Ward
A26	US- 6,300,065	10/9/01	Kieke <i>et al.</i>

A27	US-	6,331,391	12/18/01	Wittrup <i>et al.</i>
A28	US-	6,423,538	7/23/02	Wittrup <i>et al.</i>
A29	US-	6,455,263	9/24/02	Payan
A30	US-	6,528,624	03/04/03	Idusogie <i>et al.</i>
A31	US-	6,538,124	03/25/03	Idusogie <i>et al.</i>
A32	US-	6,737,056	5/18/04	Presta
A33	US-	6,821,505	11/23/04	Ward
B01	EP 0	327 378	0809/89	Trustees of Columbia University
B02	WO 88/07089		09/22/88	Medical Research Council
B03	WO 89/07142		08/10/89	Morrison, S.
B04	WO 92/16562		10/01/92	Lynxvale Limited
B05	WO 93/22332		11/11/93	Board of Regents, Univ. Texas Sys
B06	WO 94/18330		8/18/94	Unilever PLC
B07	WO 94/29351		12/22/94	Morgan, S. <i>et al.</i>
B08	WO 95/05468		02/23/95	Lynxvale Limited
B09	WO 97/28267		08/07/97	Repligen Corporation
B10	WO 97/34631		09/25/97	Board of Regents, Univ. Texas Sys
B11	WO 97/44362		11/27/97	Protein Design Labs, Inc.
B12	WO 98/05787		02/12/98	Bristol-Myers Squibb Company
B13	WO 98/23289		06/04/98	The General Hospital Corporation
B14	WO 98/52975		11/26/98	Dutches Krebsforschungszentrum Stiftung Des Oeffentlichen Rechts
B15	WO 99/43713		09/02/99	Lexigen Pharmaceuticals Corp.
B16	WO 99/51642		10/14/99	Genentech, Inc
B17	WO 99/58572		11/18/99	Cambridge Univ. Tech. Serv. Ltd.
B18	WO 00/09560		02/24/00	Abgenix, Inc.
B19	WO 00/42072		7/20/00	Genenetch, Inc.
B20	WO 02/060919		08/0802	Medimmune, Inc.
B21	WO 02/086070		10/31/02	Dyax Corporation, Inc.
B22	WO 03/074679		09/12/03	Xencor
B23	WO 04/029207		04/08/04	Xencor
B24	WO 04/074455		09/02/04	Applied Molecular Evolution, Inc.
B25	WO 04/099249		11/18/04	Xencor

B26	WO 05/070963	08/04/05	Applied Molecular Evolution, Inc.
B27	WO 06/020114	02/23/06	Applied Molecular Evolution, Inc.
C01	Altman <i>et al.</i> , "Phenotypic Analysis of Antigen-Specific T Lymphocytes", Science 274:94-96, 1996		
C02	Angal <i>et al.</i> , "A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody," Mol Immunol 30 :105-108, 1993		
C03	Armour <i>et al.</i> , "The contrasting IgG-binding interactions of human and herpes simplex virus Fc receptors," Biochemical Society Transactions 30:495-500, 2002		
C04	Armour <i>et al.</i> , "Recombinant human IgG molecules lacking Fc gamma receptor I binding and monocyte triggering activities," Eur J Immunol 29:2613-2624, 1999		
C05	Armour <i>et al.</i> , "Differential binding to human Fc gammaRIIa and Fc gammaRIIb receptors by human IgG1 wildtype and mutant antibodies," Mol Immunol 40 :585-593, 2003		
C145	Armstrong, S. <i>et al.</i> , "Heterogeneity of IgG1 monoclonal anti-Rh(D): an investigation using ADCC and macrophage binding assays," Brit. J. Haematol. 66:257-262 (1987)		
C06	Baggiolini M, Dewald B. "Cellular models for the detection and evaluation of drugs that modulate human phagocyte activity," Experientia. Oct 15;44(10):841-848, 1988		
C07	Boder and Wittrup, 1997, "Yeast surface display for screening combinatorial polypeptide libraries", Nature Biotechnology 15:553-557		
C08	Boder and Wittrup, "Optimal screening of surface-displayed polypeptide libraries," Biotechnol Prog 14:55-62, 1998		
C09	Boder and Wittrup, "Yeast surface display for directed evolution of protein expression, affinity, and stability," Methods in Enzymology 328:430-444, 2000		
C10	Boder <i>et al.</i> , "Directed evolution of antibody fragments with monovalent femtomolar antigen-binding affinity," Proc. Natl. Acad. Sci. USA 97:10701-10705, 2000		
C11	Bredius <i>et al.</i> , "Role of neutrophil Fc gamma RIIa (CD32) and Fc gamma RIIB (CD16) polymorphic forms in phagocytosis of human IgG1- and IgG3-opsonized bacteria and erythrocytes," Immunology 83:624-630, 1994		
C12	Brekke <i>et al.</i> , "Human IgG isotype-specific amino acid residues affecting complement-mediated cell lysis and phagocytosis," Eur J Immunol 24:2542-2547, 1994		
C13	Brown EJ., Vol. 45 (Microbes as Tools for Cell Biology) in <i>Methods In Cell Biology</i> , Russell ed. Academic Press Inc. pp.147-64, 1994		
C14	Burlmeister <i>et al.</i> , "Crystal structure of the complex of rat neonatal Fc receptor with Fc," Nature 372:379-383, 1994		
C15	Burton and Woof, "Human antibody effector function," Advances in Immunology 51:1-84, 1992		
C16	Burton <i>et al.</i> , "Molecular recognition of antibody (IgG) by cellular Fc receptor (FcRI)," Mol Immunol 25:1175-1181, 1988		
C17	Burton, "Immunoglobulin G: functional sites," Mol Immunol 22:161-206, 1985		

- C18 Canfield and Morrison, "The binding affinity of human IgG for its high affinity Fc receptor is determined by multiple amino acids in the CH2 domain and is modulated by the hinge region," *J Exp Med* 173:1483-1491, 1991
- C19 Caron *et al.*, "Engineered humanized dimeric forms of IgG are more effective antibodies," *J Exp Med* 176 :1191-5, 1992
- C20 Carter *et al.*, "Humanization of an anti-p185HER2 antibody for human cancer therapy," *Proc. Natl. Acad. Sci. USA* 89:4285-4289, 1992
- C21 Cartron *et al.*, "Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene," *Blood* 99 :754-758, 2002
- C22 Chappel *et al.*, "Identification of the Fc gamma receptor class I binding site in human IgG through the use of recombinant IgG1/IgG2 hybrid and point-mutated antibodies," *Proc. Natl. Acad. Sci USA* 88:9036-9040, 1991
- C23 Chappel *et al.*, "Identification of a secondary Fc gamma RI binding site within a genetically engineered human IgG antibody," *J Biol. Chem* 268:25124-25131, 1993
- C24 Ciccimarra *et al.*, "Localization of the IgG effector site for monocyte receptors," *Proc. Natl. Acad. Sci. U.S.A.* 72 :2081-2083, 1975
- C25 Clynes and Ravetch, "Cytotoxic antibodies trigger inflammation through Fc receptors," *Immunity* 3:21-26, 1995
- C26 Clynes *et al.*, "Modulation of immune complex-induced inflammation in vivo by the coordinate expression of activation and inhibitory Fc receptors," *J Exp Med* 189:179-185, 1999
- C27 Clynes *et al.*, "Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets," *Nature Medicine* 6 :443-446, 2000
- C28 Clynes *et al.*, "Fc receptors are required in passive and active immunity to melanoma," *Proc. Natl. Acad. Sci USA* 95:652-656, 1998
- C29 Clynes *et al.*, "Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis," *Science* 279:1052-1054, 1998
- C30 de Haas, Wien Kin "IgG-Fc receptors and the clinical relevance of their polymorphisms," *Wien Klin Wochenscha* 113:825-831, 2001
- C31 Deisenhofer, "Crystallographic refinement and atomic models of a human Fc fragment and its complex with fragment B of protein A from *Staphylococcus aureus* at 2.9- and 2.8-A resolution," *Biochem.* 20:2361-2370, 1981
- C32 Deo *et al.*, "Clinical significance of IgG Fc receptors and Fc gamma R-directed immunotherapies," *Immunology Today* 18:127-135, 1997
- C33 Duncan and Winter, "The binding site for C1q on IgG," *Nature* 332 :738-740, 1988
- C34 Duncan and Winter, "Localization of the binding site for the human high-affinity Fc receptor on IgG," *Nature* 332:563-564, 1988
- C35 Flesch and Neppert, "Functions of the Fc receptors for immunoglobulin G," *J Clin Lab Anal* 14:141-156, 2000
- C36 Gergeley *et al.*, "Fc receptors on lymphocytes and K cells," *Biochemical Society Transactions* 12:739-743, 1984

- C37 Gergely and Sarmay, "The two binding-site models of human IgG binding Fc gamma receptors," *FASEB J* 4:3275-3283, 1990
- C38 Greenwood and Clark, Effector functions of matched sets of recombinant human IgG subclass antibodies". (final version edited Feb. 11, 1993)
- C39 Greenwood *et al.*, "Structural motifs involved in human IgG antibody effector functions," *Eur J Immunol* 23:1098-1104, 1993
- C40 Greenwood *et al.*, "Engineering multiple-domain forms of the therapeutic antibody CAMPATH-1H: effects on complement lysis," *Therapeutic Immunology* 1:247-255, 1994
- C41 Hadley *et al.*, "The functional activity of Fc gamma RII and Fc gamma RIII on subsets of human lymphocytes," *Immunology* 76:446-451, 1992
- C42 Hattai *et al.*, "Association of Fc gamma receptor IIIB, but not of Fc gamma receptor IIA and IIIA polymorphisms with systemic lupus erythematosus in Japanese," *Genes and Immunity* 1:53-60, 1999
- C43 Hayes, Fc Engineering to Enhance Monoclonal Antibody Effector Functions. (Presentation) Xecor, CA, 2003
- C44 Herzenberg *et al.*, "The history and future of the fluorescence activated cell sorter and flow cytometry: a view from Stanford," *Clinical Chem.* 2002;48:1819-1827, 2002
- C45 Heyman, "Regulation of antibody responses via antibodies, complement, and Fc receptors," *Annu Rev Immunol* 18:709-737, 2000
- C46 Hogarth *et al.*, "Characterization of FeR Ig-binding sites and epitope mapping," *Immunomethods* 4 :17-24, 1994
- C47 Holler *et al.*, "In vitro evolution of a T cell receptor with high affinity for peptide/MHC," *Proc. Natl. Acad. Sci. U.S.A.* 97 :5387-92, 2000
- C48 Hulett *et al.*, "Identification of the IgG binding site of the human low affinity receptor for IgG Fc gamma RII. Enhancement and ablation of binding by site-directed mutagenesis," *J. Biol. Chem.* 269:15287-15293, 1994
- C49 Hulett *et al.*, "Multiple regions of human Fc gamma RII (CD32) contribute to the binding of IgG," *J. Biol. Chem.* 270:21188-21194, 1995
- C50 Hulett *et al.*, "Chimeric Fc receptors identify functional domains of the murine high affinity receptor for IgG," *J Immunol* 147 :1863-1868, 1991
- C51 Idusogie *et al.*, "Mapping of the C1q binding site on rituxan, a chimeric antibody with a human IgG1 Fc," *J Immunol* 164: 4178-4184, 2000
- C52 Idusogie *et al.*, "Engineered antibodies with increased activity to recruit complement," *J Immunol* 166 :2571-2575, 2001
- C53 Isaacs *et al.*, "A therapeutic human IgG4 monoclonal antibody that depletes target cells in humans," *Clin Exp Immunol* 106 :427-433, 1996
- C54 Isaacs *et al.*, "Therapy with monoclonal antibodies. An in vivo model for the assessment of therapeutic potential," *J Immunol* 148 :3062-3071, 1992

- C55 Isaacs *et al.*, "Therapy with monoclonal antibodies. II. The contribution of Fc gamma receptor binding and the influence of C(H)1 and C(H)3 domains on in vivo effector function," *J Immunol* 161 :3862-3869, 1998
- C56 Jassal *et al.*, "Remodeling glycans on IgG by genetic re-engineering," *Biochem Soc Trans* 26 :S113, 1998
- C57 Jeffcris and Lund, "Interaction sites on human IgG-Fc for Fc gammaR: current models," *Immunology Letters* 82 :57-65, 2002
- C58 Jeffcris *et al.*, "Recognition sites on human IgG for Fc gamma receptors: the role of glycosylation," *Immunol Lett* 44 :111-7, 1995
- C59 Jeffcris *et al.*, "IgG-Fc-mediated effector functions: molecular definition of interaction sites for effector ligands and the role of glycosylation," *Immunol Rev* 163:59-76, 1998
- C60 Jeffcris *et al.*, "Molecular definition of interaction sites on human IgG for Fc receptors (huFc gamma R)," *Mol Immunol* 27 :1237-1240, 1990
- C61 Jendeborg *et al.*, "Engineering of Fc(1) and Fc(3) from human immunoglobulin G to analyse subclass specificity for staphylococcal protein A," *J Immunological Methods* 201 :25-34, 1997
- C62 Kadar *et al.*, "Synthetic peptides comprising defined sequences of CH-2 and CH-3 domains of human IgG1 induce prostaglandin E2 production from human peripheral blood mononuclear cells," *Immunol Lett* 32:59-63, 1992
- C63 Kadar *et al.*, "Modulatory effect of synthetic human IgG Fc peptides on the in vitro immune response of murine spleen cells," *Int J Immunopharmacol* 13 :147-55, 1991
- C64 Kato *et al.*, "Structural basis of the interaction between IgG and Fc gamma receptors," *J Mol Biol* 295:213-224, 2000
- C65 Keler *et al.*, "Differential effect of cytokine treatment on Fc alpha receptor I- and Fc gamma receptor I-mediated tumor cytotoxicity by monocyte-derived macrophages," *J. of Immunol.* 164:5746-52, 2000
- C66 Kieck *et al.*, "Selection of functional T cell receptor mutants from a yeast surface-display library," *Proc. Natl. Acad. Sci. U.S.A.* 96 :5651-56, 1999
- C67 Kim *et al.*, "Analysis of Fc gamma RIII and IgG Fc polymorphism reveals functional and evolutionary implications of protein-protein interaction," *J Mol Evol* 53:1-9, 2001
- C68 Klein *et al.*, "Expression of biological effector functions by immunoglobulin G molecules lacking the hinge region," *Proc. Natl. Acad. Sci. U.S.A.* 78 :524-528, 1981
- C69 Koene *et al.*, "Fc gamma RIIIA-158V/F polymorphism influences the binding of IgG by natural killer cell Fc gamma RIIIA, independently of the Fc gamma RIIIA-48L/R/H phenotype," *Blood* 90 :1109-1114, 1997
- C70 Kranz *et al.*, "Mechanisms of ligand binding by monoclonal anti-fluoresceyl antibodies," *J. Biol. Chem.* 257:6987-6995, 1982
- C146 Kumpel, B.M. Brit. "Human monoclonal anti-D antibodies," *J. Haematol.* 71:415-420 (1989)
- C71 Lehmann *et al.*, "Phagocytosis: measurement by flow cytometry," *J Immunol Methods.* 243(1-2):229-42, 2000

- C72 Lehmbecher *et al.*, "Variant genotypes of the low-affinity Fc gamma receptors in two control populations and a review of low-affinity Fc gamma receptor polymorphisms in control and disease populations," *Blood* 94:4220-4232, 1999
- C73 Li *et al.*, "Reconstitution of human Fc gamma RIII cell type specificity in transgenic mice," *J Exp Med* 183 :1259-1263, 1996
- C74 Liu *et al.*, "Production of a mouse-human chimeric monoclonal antibody to CD20 with potent Fe-dependent biologic activity," *J. Immunol.* 139:3521-3526, 1987
- C75 Lund *et al.*, "Expression and characterization of truncated forms of humanized L243 IgG1. Architectural features can influence synthesis of its oligosaccharide chains and affect superoxide production triggered through human Fc gamma receptor I," *Eur J Biochem* 267 :7246-57, 2000
- C76 Lund *et al.*, "Oligosaccharide-protein interactions in IgG can modulate recognition by Fc gamma receptors," *FASEB J* 9 :115-119, 1995
- C77 Lund *et al.*, "Human Fc gamma RI and Fc gamma RII interact with distinct but overlapping sites on human IgG," *J Immunol* 147 :2657-62, 1991
- C78 Lund *et al.*, "Multiple interactions of IgG with its core oligosaccharide can modulate recognition by complement and human Fc gamma receptor I and influence the synthesis of its oligosaccharide chains," *J Immunol* 157 :4963-4969, 1996
- C79 Lund *et al.*, "Multiple binding sites on the CH2 domain of IgG for mouse Fc gamma R11," *Molecular Immunology* 29:53-59, 1992
- C80 Maenaka *et al.*, "The human low affinity Fc gamma receptors IIa, IIb, and III bind IgG with fast kinetics and distinct thermodynamic properties," *J Biol Chem* 48 :44898-904, 2001
- C81 Michaelsen *et al.*, "One disulfide bond in front of the second heavy chain constant region is necessary and sufficient for effector functions of human IgG3 without a genetic hinge," *Immunology* 91 :9243-9247, 1994
- C82 Morgan *et al.*, "The N-terminal end of the CH2 domain of chimeric human IgG1 anti-HLA-DR is necessary for C1q, Fc gamma RI and Fc gamma RIII binding," *Immunology* 86 :319-324, 1995
- C83 Morrison *et al.*, "Structural determinants of IgG structure," *Immunologist* 2 :119-124, 1994
- C84 Munn *et al.*, "Phagocytosis of tumor cells by human monocytes cultured in recombinant macrophage colony-stimulating factor," *J Exp Med.* 172(1):231-7, 1990
- C85 Nagarajan *et al.*, "Ligand binding and phagocytosis by CD16 (Fc gamma receptor III) isoforms. Phagocytic signaling by associated zeta and gamma subunits in Chinese hamster ovary cells," *J Biol Chem* 270 :25762-25770, 1995
- C86 Neuberger *et al.*, "Recombinant antibodies possessing novel effector functions," *Nature* 312 :604-608, 1984
- C87 Norderhaug *et al.*, "Chimeric mouse human IgG3 antibodies with an IgG4-like hinge region induce complement-mediated lysis more efficiently than IgG3 with normal hinge," *Eur J Immunol* 21:2379-84, 1991
- C88 Nose and Leanderson, "Substitution of asparagine324 with aspartic acid in the Fc

- portion of mouse antibodies reduces their capacity for C1q binding," *Eur J Immunol* 19 :2179-81, 1989
- C89 Okazaki *et al.*, "Fucose depletion from human IgG1 oligosaccharide enhances binding enthalpy and association rate between IgG1 and FcgammaRIIIa," *J Mol Biol* 336 :1239-1249, 2004
- C90 Orlao and Ruiz-Arguelles, "General concepts about cell sorting techniques," *Clinical Biochem.* 29:5-9, 1996
- C91 Partridge *et al.*, "The use of anti-IgG monoclonal antibodies in mapping the monocyte receptor site on IgG," *Mol Immunol.* 23(12):1365-72, 1986
- C92 Perussia "Human Natural Killer Cell Protocols" in *Methods Molecular Biology.* vol. 121 (Campbell *et al.* eds.) Humana Press Inc., Totowa, NJ. 179-92, 2000
- C93 Radaev and Sun, "Recognition of immunoglobulins by Fcgamma receptors," *Molecular Immunology* 38 :1073-1083, 2001
- C94 Ravetch and Bolland, "IgG Fc receptors," *Annu Rev Immunol* 19:275-90, 2001
- C95 Ravetch and Clynes, "Divergent roles for Fc receptors and complement in vivo," *Annu Rev Immunol* 16:421-432, 1998
- C96 Ravetch and Kinet, "Fc receptors," *Annu Rev Immunol* 9:457-492, 1991
- C97 Ravetch and Lanier, "Immune inhibitory receptors," *Science* 290:84-89, 2000
- C98 Redpath *et al.*, "The influence of the hinge region length in binding of human IgG to human Fcgamma receptors," *Hum Immunol* 59 :720-727, 1998
- C99 Reff *et al.*, "Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20," *Blood* 83:435-445, 1994
- C100 Riechmann *et al.*, "Reshaping human antibodies for therapy," *Nature.* 332(6162):323-7, 1988
- C101 Sarmay *et al.*, "The effect of synthetic peptides corresponding to Fc sequences in human IgG1 on various steps in the B cell activation pathway," *Eur J Immunol* 18 :289-294, 1988
- C102 Sarmay *et al.*, "Ligand inhibition studies on the role of Fc receptors in antibody-dependent cell-mediated cytotoxicity," *Mol Immunol* 21 :43-51, 1984
- C103 Sarmay *et al.*, "Mapping and comparison of the interaction sites on the Fc region of IgG responsible for triggering antibody dependent cellular cytotoxicity (ADCC) through different types of human Fc gamma receptor," *Mol Immunol* 29 :633-639, 1992
- C104 Sautes-Fridman *et al.*, "Fc gamma receptors: a magic link with the outside world," *ASHI Quarterly*, 4th Quarter:148-151, 2003
- C105 Schaffner *et al.*, "Chimeric interleukin 2 receptor alpha chain antibody derivatives with fused mu and gamma chains permit improved recruitment of effector functions," *Mol Immunol* 32 :9-20, 1995 (Erratum in 32 :1299, 1995)
- C106 Schatz *et al.*, "Use of peptide libraries to map the substrate specificity of a peptide-modifying enzyme: a 13 residue consensus peptide specifies biotinylation in *Escherichia coli*," *Bio/Technology* 11:1138-1143, 2000

- C107 SENSEL *et al.*, "Amino acid differences in the N-terminus of C(H)2 influence the relative abilities of IgG2 and IgG3 to activate complement," *Molecular Immunology* 34:1019-1029, 1997
- C108 SHIELDS *et al.*, "High resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII, and FcRn and design of IgG1 variants with improved binding to the Fc gamma R," *J Biol Chem* 276 :6591-6604, 2001
- C109 SHOPES *et al.*, "Recombinant human IgG1-murine IgE chimeric Ig. Construction, expression, and binding to human Fc gamma receptors," *J Immunol* 145 :3842-3848, 1990
- C110 SHOPES, "A genetically engineered human IgG mutant with enhanced cytolytic activity," *J Immunol* 148 :2918-2922, 1992
- C111 SHOPES, "A genetically engineered human IgG with limited flexibility fully initiates cytotoxicity via complement," *Molecular Immunology* 30 :603-609, 1993
- C112 SHUSTA *et al.*, "Yeast polypeptide fusion surface display levels predict thermal stability and soluble secretion efficiency," *J Mol Biol* 292:949-956, 1999
- C113 SHUSTA *et al.*, "Increasing the secretory capacity of *Saccharomyces cerevisiae* for production of single-chain antibody fragments," *Nature Biotechnology* 16:773-777, 1998
- C114 SHUSTA *et al.*, "Directed evolution of a stable scaffold for T-cell receptor engineering," *Nature Biotechnology* 18:754-759, 2000
- C115 SMITH and MORRISON, "Recombinant polymeric IgG: an approach to engineering more potent antibodies," *Bio/Technology* 12:683-688, 1994
- C116 SONDERMANN and OOSTHUIZEN, "The structure of Fc receptor/Ig complexes: considerations on stoichiometry and potential inhibitors," *Immunology Letters*, 82:51-56, 2002
- C117 SONDERMANN *et al.*, "Molecular basis for immune complex recognition: a comparison of Fc-receptor structures," *J. Mol. Biol.* 309:737-749, 2001
- C118 SONDERMANN *et al.*, "Crystal structure of the soluble form of the human fcgamma-receptor IIb: a new member of the immunoglobulin superfamily at 1.7 Å resolution," *EMBO J* 18:1095-1103, 1999
- C119 SONDERMANN *et al.*, "The 3.2-Å crystal structure of the human IgG1 Fc fragment-Fc gammaRIII complex," *Nature* 406:267-273, 2000
- C120 STEPLEWSKI *et al.*, "Biological activity of human-mouse IgG1, IgG2, IgG3, and IgG4 chimeric monoclonal antibodies with antitumor specificity," *Proc. Natl. Acad. Sci. U.S.A.* 85:4852-4856, 1988
- C121 STROHMCIER *et al.*, "Role of the Fc gamma R subclasses Fc gamma RII and Fc gamma RIII in the activation of human neutrophils by low and high valency immune complexes," *J Leukocyte Biol* 58:415-422, 1995
- C122 SYLVESTRE and RAVETCH, "A dominant role for mast cell Fc receptors in the Arthus reaction," *Immunity* 5:387-390, 1996
- C123 SYLVESTRE and RAVETCH, "Fc receptors initiate the Arthus reaction: redefining the inflammatory cascade," *Science* 265:1095-1098, 1994

- C124 Takai *et al.*, "FcR gamma chain deletion results in pleiotrophic effector cell defects," *Cell* 76 :519-529, 1994
- C125 Takai *et al.*, "Augmented humoral and anaphylactic responses in Fc gamma RII-deficient mice," *Nature* 379:346-349, 1996
- C126 Takai, "Roles of Fc receptors in autoimmunity," *Nature Reviews* 2:580-592, 2002
- C127 Tamm *et al.*, "The IgG binding site of human FcγRIIIB receptor involves CC' and FG loops of the membrane-proximal domain," *J Biol Chem* 271:3659-3666, 1996
- C128 Tao *et al.*, "The differential ability of human IgG1 and IgG4 to activate complement is determined by the COOH-terminal sequence of the CH2 domain," *J Exp Med* 173:1025-1028, 1991
- C129 Tao *et al.*, "Structural features of human immunoglobulin G that determine isotype-specific differences in complement activation," *J Exp Med* 178:661-667, 1993
- C130 Van Sorge *et al.*, "FcγgammaR polymorphisms: Implications for function, disease susceptibility and immunotherapy," *Tissue Antigens* 61:189-202, 2003
- C131 VanAntwerp and Wittrup, "Fine affinity discrimination by yeast surface display and flow cytometry," *Biotechnol Prog* 16:31-37, 2000
- C132 Vidarte, "Serine 132 is the C3 covalent attachment point on the CH1 domain of human IgG1," *J Biol Chem* 276:38217-38233, 2001
- C133 Ward and Ghetie, "The effector functions of immunoglobulins: implications for therapy," *Therapeutic Immunology* 2:77-94, 1995
- C134 Weng and Levy, "Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma," *J Clin Oncol* 21:3940-3947, 2003
- C147** Wiener, E. *et al.* "Differences between the activities of human monoclonal IgG1 and IgG3 anti-D antibodies of the Rh blood group system in their abilities to mediate effector functions of monocytes," *Immunol.* 65:159-163 (1988)
- C135 Wing *et al.*, "Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: Involvement of CD16 (FcγRIII) and CD11a/CD18 (LFA-1) on NK cells," *J Clin Invest* 98 :2819-2826, 1996
- C136 Wingren *et al.*, "Comparison of surface properties of human IgA, IgE, IgG and IgM antibodies with identical and different specificities," *Scand J Immunol* 44:430-436, 1996
- C137 Wittrup, "The single cell as a microplate well," *Nat Biotechnol* 18:1039-1040, 2000
- C138 Wittrup, "Protein engineering by cell-surface display," *Curr. Opin. Biotechnol.* 12:395-399, 2001
- C139 Woolf *et al.*, "Localisation of the monocyte-binding region on human immunoglobulin G," *Mol Immunol* 23 :319-330, 1986
- C140 Wu *et al.*, "a novel polymorphism of FcγRIIIa (CD16) alters receptor function and predisposes to autoimmune disease," *J Clin Invest* 100 :1059-1070, 1997
- C141 Xu *et al.*, "Residue at position 331 in the IgG1 and IgG4 CH2 domains contributes to their differential ability to bind and activate complement," *J Biol Chem* 269 :3469-

3474, 1994

- C142 Yeung and Wittrup, "Quantitative screening of yeast surface-displayed polypeptide libraries by magnetic bead capture," *Biotechnol Prog* 18:212-220, 2002
- C143 Zeidler *et al.*, "The Fc-region of a new class of intact bispecific antibody mediates activation of accessory cells and NK cells and induces direct phagocytosis of tumour cells," *British J Cancer* 83:261-266, 2000
- C144 Zuckier *et al.*, "Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life," *Cancer Res* 58 :3905-3908, 1998

This Information Disclosure Statements is being submitted prior to an Initial Office Action. No fee is accordingly believed due for consideration of this Information Disclosure Statement. However, if the Commissioner determines that an additional fee is required in for consideration of this Information Disclosure Statement, the U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to Deposit Account No. **05-0460** referencing docket number **0301.0004C**.

The submission of the listed and appended documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

Applicant respectfully requests that the documents listed on the accompanying Form SB08 be considered and made of record in the present application. Applicant further requests that the Examiner initial and return a copy of the enclosed PTO SB08 form and indicate in the official file wrapper of this patent application that the documents have been considered.

While the listed references are considered relevant to the prosecution of the present application, it is submitted that the references, either alone or in combination, do not detract from the patentability of the claimed invention.

Respectfully Submitted,

Date: **December 7, 2006**
Edell, Shapiro & Finnan, LLC
1901 Research Blvd., Suite 400
Rockville, MD 20850
Telephone: (301) 424-3640
Facsimile: (301) 762-4056

/Jeffrey I. Auerbach/
Jeffrey I. Auerbach
Registration No. 32,680
Attorney for Assignee